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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/663,189 | 09/15/2003 | William G. Nelson | JHU1660-2 | 3983 |

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| EXAMINER | |
|---|---|
| SITTON, JEHANNE SOUAYA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 03/26/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/663,189 | NELSON ET AL. | |
| | Examiner | Art Unit | |
| | Jehanne S. Sitton | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *76-83,86 and 87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-83, 86 and 87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. The election of species requirement made in the previous office action is withdrawn. Accordingly, claims 76-83 and 86-87 are examined herein. Claims 1-75 and 84-85 are canceled.

### *Claim Objections*

2. Claim 77 is objected to for the following informalities. In claim 77, the recitation of "regent" is misspelled and should be amended to recite --reagent--.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 80, 83 and 86-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76 has been amended to be drawn to a kit comprising primer pairs (plural), however claim 80 is drawn to a single primer pair. It is unclear, therefore, if claim 76 is drawn to more than 2 primers, although it recites pairs (plural).

Claim 83 recites "primers", but it is dependent from claim 81 which is drawn to a kit which is confusing because it is not clear that the claim intends to limit the primers in the kit from which claim 81 depends. This can be overcome by amending claim 83 to recite "the kit of claim 83, wherein the primers are...". Claim 83 also recites "as shown in" however it is not

clear if this embodiment is meant to encompass sequences within SEQ ID NOS 1 and 2. This rejection can be overcome by reciting instead "wherein the primers are SEQ ID NOS 1 and 2".

Claims 86 and 87 recite the term "using" whereas the claims are drawn to kits or primers respectively. The term "using" renders the claims indefinite as it appears to be drawn to a method step, which is not set forth in either claims 80 or 82. It is therefore unclear, how claims 86 and 87 further limit the claims from which they depend. It is not clear if they are additional reagents in the kits and primers of claims 76 and 82 respectively, or whether they further define the primers set forth in claims 76 and 82.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 76-79 and 81-82 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Herman I (Herman et al; US Patent 6,017,704).

With regard to claim 76, Herman I teaches and claims (claims 15-22 of Herman) kits for amplification of the promoter of GST-pi (GSTP1) for the purpose of detecting CpG methylation. The kits taught by Herman I comprise a carrier means being compartmentalized to receive in

close confinement therein, one or more containers (see col. 18, lines 53-59). Herman I teaches that one container contains a reagent that modifies unmethylated, such as sodium bisulfite (instant claims 77 and 78) and a second container can contain primers for amplification of CpG containing nucleic acids. Herman I teaches primers which can distinguish between methylated and unmethylated nucleic acid for the promoter of GSTP1 (see cols 13-18 and table 2). With regard to claims 79 and 82, the claim recites the primer hybridizes with a target polynucleotide sequence having the sequence in the region of about –539 to –239 (which corresponds to about positions 690-985 of Genbank Accession numbers X08058, used in the instant specification and Herman). Herman I teaches primers that hybridize at positions 1078 and 1082 (table 2). This inherently anticipates claims 79 and 82 as the term 'having' has been broadly interpreted as comprising, thus the primers hybridize to a target sequence that comprises the positions indicated in the claim. Additionally, the specification does not define the limits of the term 'about', and therefore positions 1078 and 1082 are broadly interpreted to be a region that corresponds to "about –539 to –239 upstream from the GSTP1 transcription start site". With regard to claim 81, Herman I teaches that the kit further comprises nucleic acid amplification buffer (see sentence bridging cols 18 and 19).

7. Claims 82 and 87 are rejected under 35 U.S.C. 102(a) as being anticipated by Tchou (Tchou et al; International Journal of Oncology, vol. 16, pages 663-676, 2000).

Tchou teaches a method of detection of GSTP1 island hypermethylation using primers which hybridize with a target polynucleotide sequence having the sequence in the region the region from about –539 to –239 upstream of the GSTP1 transcription start site (see page 865,

col. 2). The claims have not been awarded benefit of priority to the provisional application 60/159,168, as the application does not provide support for broadly any primers which would hybridize to the indicated region. Claim 87 as been broadly interpreted to encompass additional primers to those claimed in claim 82.

8. Claim 82 is rejected under 35 U.S.C. 102(b) as being anticipated by Clark (Clark et al; WO 99/55905).

Clark teaches primers for the detection of the methylated CpGs in the promoter of GSTP1. With regard to claim 82, Clark teaches primers which selectively amplify the methylated sequence (see table 3, page 42, SEQ ID NOS 3-5, 10-12). These primers amplify CpG islands in a target polynucleotide having the sequence from about –539 to –239 upstream from the GSTP1 transcription start site (which corresponds to about positions 690-985 of Genbank Accession numbers X08058 and M24485). The coordinates in table 3 correspond to Genbank Accession numbers M24485 and X08058.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 76-81, 83, and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tchou in view of Herman II (Herman et al; US Patent 5,786,146). The claims have not been awarded benefit of priority to the provisional application 60/159,168, as the application does not provide support for kits.

Tchou teaches a method of detection of GSTP1 island hypermethylation using primers which hybridize with a target polynucleotide sequence having the sequence in the region from about –539 to –239 upstream of the GSTP1 transcription start site (see page 865, col. 2). Tchou teaches sodium bisulfite as well as amplification buffer. Tchou does not teach packaging the primers and reagents into kit format, however Herman II teaches packaging biochemical reagents for PCR amplification and analysis of methylated CpG nucleotides. Hermann II teaches kits including carrier means being compartmentalized in close confinement therein, one or more containers (col. 10, lines 59-67), wherein one container contains bisulfite (a reagent for modifying unmethylated cytosines) and a second container containing primers which distinguish between modified methylated and unmethylated nucleic acids (claim 22 of Hermann II). Hermann II teaches the kits can further comprise amplification buffer. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to

package the reagents taught by Tchou in kit format for the purpose of providing premade reagents as taught by Hermann II.

12. Claims 76-81 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark in view of Herman II.

Clark teaches an assay for detection of methylated CpGs in the promoter of GSTP1 (see table 3, figure 1) using bisulfite (claims 77-78) and methylation specific primers (see pages 4-5) for PCR. With regard to claim 79, Clark teaches primers which selectively amplify the methylated sequence (see table 3, page 42, SEQ ID NOS 3-5, 10-12). These primers amplify CpG islands in a target polynucleotide having the sequence from about –539 to –239 upstream from the GSTP1 transcription start site (which corresponds to about positions 690-985 of Genbank Accession numbers X08058 and M24485). The coordinates in table 3 correspond to Genbank Accession numbers M24485 and X08058.

Clark does not teach packaging the reagents in kit format, however Herman II teaches packaging biochemical reagents for PCR amplification and analysis of methylated CpG nucleotides. Hermann II teaches kits including carrier means being compartmentalized in close confinement therein, one or more containers (col. 10, lines 59-67), wherein one container contains bisulfite (a reagent for modifying unmethylated cytosines) and a second container containing primers which distinguish between modified methylated and unmethylated nucleic acids (claim 22 of Hermann II). Hermann II teaches the kits can further comprise amplification buffer. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at

the time the invention was made to package the reagents and primers taught by Clark in kit format for the purpose of providing premade reagents as taught by Hermann II.

With regard to claims 80 and 83, Clark does not teach using primers with SEQ ID NOS 1 and 2 or sequences within SEQ ID NOS 1 and 2, however Clark specifically teaches amplifying a target region including CpG sites –43 to –14 (see figure 1, page 8) and to avoid primers which are influenced by sites –36, -33 and –32 (page 8, line 20 and page 10, line 4). Clark also teaches an amplicon of 499 bases, using a pair of primers, the reverse primer of which overlaps with instant SEQ ID NO: 2 (see Figure 1 first box titled "5' Flanking Promoter PCR"; SEQ ID NO 1 overlaps with position 690-716 and CpG's –45 and –44, and SEQ ID NO 2 overlaps with positions 959-985, as well as the reverse primer used to generate the amplicon). Further, Clark teaches criteria for designing primers (pages 16-17) and teaches, for example, differential methylation between PC-3 and BC, CC, and DC (figure 3B), which includes CpG's –45 to –30 (see figure 3B). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate numerous primer pairs for analysis of methylation of CpG's in the GST-Pi promoter as taught by Clark, and package them in kits as taught by Hermann II. The ordinary would have been motivated to arrive at a number of different primer pairs, including sequences within as well as consisting of SEQ ID NOS 1 and 2, for analysis of methylation profiles of CpG dinucleotides in the promoter of GST-Pi as taught by Clark.

***Double Patenting***

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 76-79 and 81-82 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-22 of U.S. Patent No. 6,017,704. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are coextensive in scope.

With regard to claim 76, claims 15-22 of the '704 patent are drawn to kits for amplification of the promoter of GST-pi (GSTP1) for the purpose of detecting CpG methylation. The kits comprise a carrier means being compartmentalized to receive in close confinement therein, one or more containers, where one container contains a reagent that modifies unmethylated, such as sodium bisulfite (instant claims 77 and 78) and a second container can contain primers for amplification of CpG containing nucleic acids. The '704 patent teaches primers which can distinguish between methylated and unmethylated nucleic acid for the promoter of GSTP1 (see cols 13-18 and table 2). With regard to claims 79 and 82, the claim recites the primer hybridizes with a target polynucleotide sequence having the sequence in the region of about –539 to –239 (which corresponds to about positions 690-985 of Genbank

Accession numbers X08058, used in the instant specification and the '704 patent). The specification does not define the limits of the term 'about', and therefore positions 1078 and 1082 are broadly interpreted to be a region that corresponds to "about –539 to –239 upstream from the GSTP1 transcription start site". With regard to claim 81, claim 20 of the '704 patent is drawn to a kit which further comprises nucleic acid amplification buffer.

15. Claims 80, 83, 86 and 87 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-22 of U.S. Patent No. 6,017,704 in view of Tchou. The claims of '704 are set forth above. The claims do not teach the primers set forth in claims 80, 83 however Tchou teaches these primers in method of analyzing GSTP1 promoter methylation. Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to arrive at kits as set forth in the '704 patent containing the primers taught by Tchou for the purpose of providing premade reagents for analyzing GSTP1 promoter methylation.

16. Claims 80 and 83 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-22 of U.S. Patent No. 6,017,704 in view of Clark.

The claims of '704 are set forth above. The claims do not teach using primers with SEQ ID NOS 1 and 2, however Clark specifically teaches amplifying a target region including CpG sites –43 to –14 (see figure 1, page 8) and to avoid primers which are influenced by sites –36, -33 and –32 (page 8, line 20 and page 10, line 4). Clark also teaches an amplicon of 499 bases, using a pair of primers, the reverse primer of which overlaps with instant SEQ ID NO: 2 (see

Figure 1 first box titled "5' Flanking Promoter PCR"; SEQ ID NO 1 overlaps with position 690-716 and CpG's –45 and –44, and SEQ ID NO 2 overlaps with positions 959-985, as well as the reverse primer used to generate the amplicon). Further, Clark teaches criteria for designing primers (pages 16-17) and teaches, for example, differential methylation between PC-3 and BC, CC, and DC (figure 3B), which includes CpG's –45 to –30 (see figure 3B). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to generate numerous primer pairs for analysis of methylation of CpG's in the GST-Pi promoter as taught by Clark. The ordinary would have been motivated to arrive at a number of different primer pairs, including SEQ ID NOS 1 and 2,for analysis of methylation profiles of CpG dinucleotides in the promoter of GST-Pi as taught by Clark.

***Conclusion***

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634

3/19/07